Systems, Devices, and Methods for Aseptic Processing

Cross-Reference to Related Applications

[1] This application claims priority to and incorporates by reference herein in its entirety, pending United States Provisional Patent Application Serial No. 60/420,691 (Applicant Docket No. 00100-01), titled "Aseptic Liquid Filler Apparatus and Related Method Thereof", filed 23 October 2003.

Brief Description of the Drawings

[2] A wide array of potential embodiments can be better understood through the following detailed description and the accompanying drawings in which:

[3] **FIG. 1** is a block diagram of an exemplary embodiment of system 1000;

[4] **FIG. 2** is a top view of an exemplary embodiment of system 2000;

[5] **FIG. 3** is a front view of an exemplary embodiment of a container positioning system 3000;

[6] **FIG. 4** is a block diagram of an exemplary embodiment of an information device 4000;

[7] **FIG. 5** is a flow chart of an exemplary embodiment of a method 5000;

[8] **FIG. 6** is a top view of an exemplary embodiment of a container positioning system 6000;

[9] **FIG. 7** is a front view of an exemplary embodiment of a Rivard shuttle 6100;

[10] **FIG. 8** is a top view of an exemplary embodiment of a stationary rail 6300;

[11] **FIG. 9** is a top view of an exemplary embodiment of a guardrail 6400; and

[12] **FIG. 10** is a top view of an exemplary embodiment of a rod 6200.

Definitions

[13] When the following terms are used herein, the accompanying definitions apply:

[14] **airflow** - a substantially unidirectional current of gas that is substantially aimed at the critical zone during operation. An airflow can comprise an inert gas, such as nitrogen, argon, etc., filtered air, such as HEPA filtered

air, etc. An airflow can be substantially linear, substantially laminar, and/or without substantial turbulence.

[15] **aseptic** - free of or using methods to keep free of pathological microorganisms; sterile.

[16] **autoclaveable** - capable of functioning normally, and designed to function normally, after sterilization via a moist heat autoclave.

[17] **clean** - devoid of contaminants. For example, a clean container can be devoid of chemical and/or biological contaminants that might jeopardize the efficacy and/or safety of a filling to be stored therein.

[18] **closure** - a device for enclosing an opening of a container or for securing another closure. Examples of a closure include a stopper, syringe plug, cap, metallic overlay cap for a stopper, etc.

[19] **container** - an enclosure for a filling having a closable opening via which the filling can be introduced. Examples of a container include a vial, syringe, bottle, etc.

[20] **container positioner** - a device for imparting directionally and temporally controlled motion to containers to transport the containers to, through, and/or from one or more processing stations.

[21] **contaminant** - an undesired chemical and/or biological material. Examples include particulates, microbes, bacteria, viruses, mold spores, disinfectant residue, etc. Contaminants can be airborne or residing on a surface.

[22] **contaminant generator** - a source of greater than a predetermined number of contaminant particles and/or droplets per cubic meter in a size range of about 0.3 micron and larger to about 0.5 micron and larger when counted at representative locations not more than 1 foot away from the critical zone, within the airflow, during filling or closing operations. For a Class 100 (ISO 5, per ISO 14644-1) contaminant generator, the predetermined number of contaminants is 3520. For a Class 1000 contaminant generator, the predetermined number is 35,200. For a Class 10,000 contaminant generator, the predetermined number is 352,000. For a Class 100,000 contaminant generator, the predetermined number is 3,520,000. Examples include mechanical, hydraulic, pneumatic, and/or

electrical parts, stored containers, and/or stored closures that experience friction (e.g., rub, slide, grind, abrade, and/or wear), vibration, leakage, and/or condensation, thereby generating at least microscopic particles and/or droplets therefrom. Other examples include unfiltered air sources that can enter the critical zone during operation; human operators that, during operation, can shed skin cells, fibers, dust, etc., exhale droplets of saliva and/or mucus, etc.; structural supports and/or machine components below the critical zone that can substantially impede the airflow, cause substantial turbulence in the airflow, and/or harbor and release contaminants and/or spilled filling. A Class 100 contaminant generator can provide more than one colony forming unit per 10 cubic feet of air from the airflow.

[23] **critical zone** - a volume within which, during operation, a container is directly exposed to the airflow, and which is defined by an entry position of the container into, and an exit position of the container from, one or more processing locations at which (1) a filling is introduced to the container via a filling opening, and (2) the filling opening is at least partially covered by a closure, and all positions of the container therebetween the entry and exit positions.

[24] **decontaminateable** - capable of being decontaminated without the use of chemical disinfectants and via insertion into a washer or sterilizer (e.g., moist heat, dry heat, gas, radiation, etc.) to meet a predetermined standard prior to or subsequent to operation. For example, a system and/or device can be decontaminateable to meet the FDA's "Industry Guideline on Sterile Drug Products Produced by Aseptic Processing" (June 1987), the FDA's "Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice" (Draft - August 2003), 21 CFR parts 210 and 211, and/or 21 CFR parts 600 through 680, all of which are incorporated by reference herein in their entirety. A decontaminateable filling system can, for example, fit within a standard laboratory hood, manually portable by a single human of average strength, evacuable, autoclaveable, and/or moist heat sterilizable.

[25] **fill** - to introduce a filling to a container during operation. A container need not be completely filled.

[26] **filling** - an intended content of a container subsequent to a fill operation. A filling can be a pharmaceutical, parenterals, biological, growth media, medicament, chemical, radioactive, cosmetic, food product, beverage, powder, solid, liquid, slurry, gas, vapor, mixture, etc. A filling is generally not intended to comprise a contaminant.

[27] **non-electrically-driven** - driven by other than an electrical motor or other electrical device. For example, driven by a fluidic, hydraulic, pneumatic, and/or magnetic system, device, and/or power source, which itself could be driven by an electrical device.

[28] **particulate** - contaminant particles, typically generated during operation. Examples include particles generated and/or provided by a mechanical, hydraulic, pneumatic, and/or electrical machine component, human operator, unfiltered air source, etc.

[29] **shield** - when used as a verb, to prevent direct impingement by the airflow and/or airborne contaminants during operation.

[30] **sterile** - devoid of living biological contamination; a subset of clean.

[31] **upstream** - between a source of the airflow and the critical zone. The source can be, for example, a hood, a duct, an outlet, a diffuser, and/or a filter, etc. that directs the airflow at the critical zone.

Publications

[32] The following U.S. Patents are hereby incorporated by reference herein in their entirety:

6,385,943	Yuyama et al.
6,308,494	Yuyama et al.
6,115,996,	Yuyama et al.
5,946,883	Yuyama et al.
5,979,515	Olsson
5,765,342	Jensen et al.
5,678,393	Yuyama et al.
5,673,535	Jagger

RE37,471	Jagger
RE37,829	Charhut et al.
5,746,042	Lombardi
5,798,020	Coughlin et al.

Detailed Description

[33] Many pharmaceuticals are injected directly into the patient's body. While this method can quickly expose the body to the drug, it also can subject the body to any contaminants found within the drug container. Manufacturers of injectable drugs (parenterals) can strive for assurance of the sterility and purity of these products. Specific contaminates can include surface and air borne microbes, particulates, and residue from prior uses and/or cleanings.

[34] A parenteral drug can be rendered sterile by: 1) terminal sterilization, and/or 2) filter sterilization followed by aseptic filling. Terminally sterilizing a parenteral drug after filling into its final container is similar to canning food. The container is subjected to high heat to sterilize its sealed contents. When the parenteral drug (usually bio-pharmaceuticals or biologic-based drugs) cannot withstand the high temperatures, the drug can be filter-sterilized prior to aseptic filling into its final container. Because there is no terminal sterilization, any recontamination of the parenteral drug during filling will likely remain with the drug.

[35] Guidelines for aseptic processing of parenteral drugs are provided in the Federal Food and Drug Administration's (FDA) "Guideline on Sterile Drug Products Produced by Aseptic Processing" (June 1987) and/or the FDA's "Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice" (Draft - August 2003), both of which are incorporated by reference herein in their entirety.

[36] To meet and/or exceed these guidelines, the drug and/or the components (containers, closures, and/or filling lines, etc.) that come in contact with the drug can be cleaned, sterilized, and protected. In addition, equipment surfaces in the vicinity of the product and the product contact components can be decontaminated. Sterile, particulate-free, laminar air (HEPA) can be flushed (e.g., down from above, up from below, horizontally, and/or diagonally, etc.)

upon these surfaces to cleanse the area. The sterile air can have a velocity of from about 50 to about 150 feet per minute, including all values and subranges therebetween, such as from about 70 to about 110 fpm, etc. Operators can be gowned in sterile garments and trained to minimize contact with these critical areas. Threats to this environment can include inadequately decontaminated and disinfected equipment, particulate generation by the equipment, and/or mishaps in the filling process that spread contamination or require excessive intervention by an operator.

[37] **FIG. 1** is a block diagram of an exemplary embodiment of a container filler system 1000, which can comprise any of various components, subsystems, and/or subassemblies. For example, container filler system 1000 can comprise a container supplier and/or container supply subsystem and/or subassembly 1100 that provides containers to a base unit and/or container filler and/or container filling subsystem 1200. Once filled, a closure supplier and/or closure supply subsystem 1300 can provide a closure that can be used to close the container. Once filled and closed, the containers can be provided to a container packaging subsystem 1400. Filtered air can be provided to the container filling subsystem 1200 by a filtered gas subsystem 1500 (e.g., air, nitrogen, oxygen, etc.). A filling can be provided to the containers by a filling pumping system 1600. A non-electrical power subsystem 1800 can operate at least a portion of container filling subsystem 1200. A programmable control system 1700, which can comprise an information device, such as for example a programmable logic controller (PLC), can control any of container supply subsystem 1100, container filling subsystem 1200, closure supply subsystem 1300, container packaging subsystem 1400, filtered air subsystem 1500, filling pumping system 1600, power subsystem 1800. Container supply subsystem 1100, container filling subsystem 1200, and/or closure supply subsystem 1300 can be positioned in an operating zone 1800.

[38] Certain exemplary embodiments of system 1000 can have utility for filling containers with pharmaceuticals, biologicals, growth media, food products, cosmetics, flavorings, essences, clinical fills, bio-hazardous materials, and/or cytotoxic materials. Certain exemplary embodiments can be useful to handlers of chemical and/or nuclear materials.

[39] In certain exemplary embodiments, container supply subsystem and/or closure supply subsystem 1300 can be integral to container filling subsystem 1200. In certain exemplary embodiments, container filling subsystem 1200 can be implemented as a bench-top apparatus that can be relatively easily disassembled, decontaminated, sterilized, and/or reassembled and can preserve the purity and/or sterility of a liquid drug product.

[40] Certain exemplary embodiments of container filling subsystem 1200 can be suitable for an open class 100 clean room, a biohazard hood, and/or an isolator glove-box. Certain exemplary embodiments of container filling subsystem 1200 can be relatively small (e.g., about 18" deep by about 28" wide by about 48" tall, but not limited thereto). Certain exemplary embodiments of container filling subsystem 1200 can weigh less than from about 10 pounds to about 300 pounds (including all values therein, such as about 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 200, and/or 250 pounds, etc., and subranges therein, such as from about 25 to about 45 pounds, from about 30 to about 55 pounds, etc.). Certain exemplary embodiments of container filling subsystem 1200 can be manually disassembleable, manually transportable, manually loadable in an autoclave, and/or manually assembleable. Certain exemplary embodiments of container filling subsystem 1200 can be pneumatically-operated. Certain exemplary embodiments of container filling subsystem 1200 can include a clear shield to shelter the container path, filling zone, closing zone, and/or critical zone from the mechanical parts. The mechanical parts can be designed to avoid particulate generating and/or microbial-harboring elements. To further protect the product and/or product components, certain exemplary embodiments can have no hinged and/or particulate generating parts and/or contaminant generators in, above, below, upstream, and/or downstream of, the critical zone.

[41] In certain exemplary embodiments, container filling subsystem 1200 can be placed in a washer to decontaminate and then inserted in an autoclave. This can generate considerably greater assurance than hand wiping and rinsing that container filling subsystem 1200 is decontaminated and sterile, without the potential introduction chemical disinfectant residues. Container filling subsystem 1200 can then be moved under a laminar airflow hood or filter and unwrapped.

[42] Containers can be preloaded in container supply subsystem 1100, which can holds from about 1 to about 1000 containers, including all values and subranges therebetween. Container supply subsystem 1100 can be a carousel, vibrating bowl, and/or hopper, etc. If implemented as a carousel, the containers can be preloaded as vertical strips, encased under a "cake lid" type shield, and sterilized.

[43] Similarly, closures also can be preloaded in a closure supply subsystem 1300, which can hold from about 1 to about 1000 closures, including all values and subranges therebetween. Closure supply subsystem 1300 can be a carousel, vibrating bowl, and/or hopper, etc. If implemented as a carousel, the closures can be preloaded as vertical strips, encased under a "cake lid" type shield, and sterilized. In certain exemplary embodiments, both the container and the closure carousels can be attached and/or attachable to the base unit. Both the containers and the closures can remain protected under the cake covers, thereby potentially avoiding exposure to the operator and/or to environmental contaminates. The containers and closures can index down and can be deposited to the point of use, remaining covered until about their moment of use.

[44] Certain exemplary embodiments of subsystem 1200 allow the containers to be supported by a rail having a number of holes therethrough to decrease the resistance of the rail to the airflow impinging on the rail. For example, from about 0 to about 75 percent of the projected surface area of the rail perpendicular to the airflow can be perforated. As another example, the rail can comprise one or more horizontal round bars upon which the containers are vertically supported. As yet another example, the rail can be one or more vertically-oriented knife-edges upon which the containers are vertically supported. As still another example, in an airflow that is directed vertically upwards, the containers can be levitated by the airflow, such that no rail is needed to provide vertical support to the containers. In any event, the rail can be designed to minimize aerodynamic drag, minimize projected surface area that is perpendicular to the airflow, and/or provide a surface and/or medium upon which the container can glide and/or be slid by the container positioner. The containers can intermittently and/or continuously travel along the rail, above the floor, and/or with nothing located between the rail and the floor. That is, no mechanical

parts, motors, or pneumatic components need be located under the critical zone and/or rail. Such embodiments can allow full laminar airflow through the critical zone to keep this zone flushed with clean air. Also, such embodiments can allow spills to drop to the floor, thereby reducing and/or eliminating equipment contamination and/or facilitating cleanup.

[45] In certain exemplary embodiments, the filling can be a solution that is moved by a pump into the container via a disposable tube connected to a disposable filling needle. Because most pumps can not be adequately decontaminated and/or autoclaved, filling pumping system 1600, and/or a component pump thereof, can be located outside the critical zone, the operation zone 1900, and/or the clean room (if utilized). Although a wide range of pumps can be used with filling pumping system 1600, certain exemplary embodiments utilize a peristaltic pumping unit manufactured by Masterflex, a division of the Barnant Company (Barrington, IL). Multiple filling needles and/or stations are possible.

[46] In certain exemplary embodiments, closure supply subsystem 1300 can supply a closure to subsystem 1200 and/or to a container. In certain exemplary embodiments, closure supply subsystem 1300 and/or each closure can be located outside of the critical zone and/or the airflow upstream of the critical zone except during provision to a container. That is, only the closure and the device providing the closure to the container (a closure provider, applier, and/or inserter) need enter the airflow upstream of the critical zone. Such a closure provider, applier, and/or inserter (which can be comprised by subsystem 1200) can, for example, pick up a closure via vacuum outside the airflow upstream of the critical zone, protrude through a protective shield, affix the closure to the container, and then retract. In various embodiments, the closure provider, applier, and/or inserter and the closure can protrude through the shield and be in place prior to the container being in position for affixing of the closure, or the provider, applier, and/or inserter and closure can protrude through the shield during or after positioning of the container for affixing of the closure.

[47] Multiple closure supply subsystems 1300 are possible. For example, a first closure supply subsystem can provide, apply, and/or insert a first closure, such as a stopper, lid, and/or cap, etc., to a container, and a second closure supply subsystem can provide and/or apply a metallic overlay to the first closure.

[48] In certain exemplary embodiments, container supply subsystem 1100, container filling subsystem 1200, and/or closure supply subsystem 1300 can be operated and/or driven non-electrically by power subsystem 1700, which can comprise a fluidic, hydraulic, pneumatic, and/or magnetic power source. For example, operation of a subsystem 1100, 1200, and/or 1300 can be fully pneumatic to avoid heat generation from electric motors and allow the subsystem to be fully washed and sterilized. Moreover, pneumatic operation can enable the subsystem to be normally operated at a sufficiently low pressure to avoid damaging, breaking, and/or crushing one or more containers (the unit can just stall) and/or risk operator injury from moving parts.

[49] When operations are complete, system 1000 can be partially dismantled into its constituent subsystems and certain of those subsystems, such as for example container supply subsystem 1100, container filling subsystem 1200, and/or closure supply subsystem (but probably not container packaging subsystem 1400, filtered air subsystem 1500, filling pumping system 1600, programmable control system 1700, and/or power subsystem 1800), can be put in a washer and/or autoclaved (steam sterilized).

[50] Certain exemplary embodiments of system 1000 and/or one or more of its subsystems can allow for any of the following:

[51] compliance with the FDA "Guideline on Sterile Drug Products Produced by Aseptic Processing" (June 1987) and/or the FDA "Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice" (Draft - August 2003);

[52] preloading of containers – relatively little to no direct operator contact after sterilization;

[53] preloading of closures – relatively little to no direct operator contact after sterilization;

[54] covered containers and/or closures – relatively little to no environmental exposure to contaminants;

[55] a shielded critical zone - shielding can substantially shield open containers from environmental exposure to contaminants;

[56] open bottom - can allow laminar air flow through at least container filling subsystem 1200;

[57] open bottom - can allow product fall through to avoid collateral contamination;

[58] no tool setup – use of pegs can allow relatively fast set-up and can minimize contamination from operator and/or environmental sources;

[59] few parts – relatively quick and/or easy setup, decontamination, and/or sterilization;

[60] pneumatic drives – autoclaveable and/or can potentially reduce and/or eliminate container breakage, and thereby potentially reduce and/or eliminate broken glass and the potential contamination and/or safety issues associated therewith, and/or an unwanted spray or dripping of filling;

[61] conveyor – Rivard shuttle can be relatively clean, simple, open architecture, and/or easy to decontaminate and/or sterilize;

[62] closure insertion unit – mechanism located substantially outside the airflow directed at the critical zone;

[63] no hinges or gears in critical zone or airflow upstream of the critical zone – helps minimize contamination, decontamination, and/or sterilization issues;

[64] relatively open architecture of system 1000 and/or container filling subsystem 1200 can help avoid disruption of, and/or preserve, the substantially linear and/or laminar velocity and/or direction of the clean airflow upstream of, throughout, and/or below the critical zone.

[65] **FIG. 2** is a top view of an exemplary embodiment of a system 2000, which can comprise a container supply subsystem 2100, a container supply chute 2150, a critical zone 2200, an operation zone 2250, container positioner and/or container positioning subsystem and/or container transport and/or container transport subsystem 2300, an exterior shield 2420, and interior shield 2440, a container fill nozzle 2460, a first closure storage 2500, a first closure provider/applier/inserter 2540, second closure storage 2600, a second closure provider/applier/inserter 2640, a filled container discharge chute 2700, and/or a frame 2800, etc.

[66] Various components of system 2000 can be supported by a frame 2800, which can provide a relatively open architecture that can allow the airflow through and/or adjacent critical zone 2200 to sweep particles away from the open containers. The minimization of horizontal surfaces in frame 2800 also can facilitate the decontamination of system 2000 by eliminating many surfaces on which contaminants and/or spilled filling can accumulate. In certain exemplary embodiments, few or no electrical and/or mechanical devices are attached and/or present beneath a top portion of frame 2800.

[67] In certain exemplary embodiments, frame 2800 can comprise welded one-inch square stainless steel tubing, such as type 316L if the frame will be steam sterilized. Other materials of suitable strength and rigidity may be substituted. The general outside dimensions of frame 2800 can be about 26 inches wide by about 18 inches deep by about 6 inches high. Other dimensions and materials may be selected.

[68] Positionable, supportable, and/or mountable on frame 2800 can be a container supply subsystem 2100, which can store, protect, and/or deliver containers. Any of many potential embodiments for container supply subsystem 2100 can be utilized, such as for example, a container carousel, hopper, bowl feeder, and/or conveyor, etc. Container supply subsystem 2100 can be preloaded and covered prior to sterilization, thereby protecting the containers from handing and environmental contaminates.

[69] In certain exemplary embodiments, container supply subsystem 2100 can be implemented as a container carousel. One method of building a container carousel is using two pieces, a rack and a cover (not shown). The carousel can hold between about 1 and about 1000 containers (including all values and subranges therebetween) that can range in volume from about 1 ml to about 100 ml (including all values and subranges therebetween). The empty containers can be pre-loaded onto the carousel, with their longitudinal axis oriented horizontally and with their open ends facing outward, and the entire carousel covered prior to sterilization. If constructed of appropriate materials, the carousel can be dry heat sterilized to over 250 degrees C or moist heat sterilized to about 121 degrees C. Once sterilized, the carousel can be placed onto a container carousel plate of system 2000.

[70] The container carousel can be formed of welded 16-gage stainless steel sheet, preferably type 316L if the carousel will be steam sterilized. Other materials of suitable strength and rigidity may be substituted. The carousel can be ringed with vertical slots that can hold empty containers. The base of the carousel can be a solid disk with the exception of one portal that can allow the containers to drop through. After a vertical row has emptied of containers, the carousel can index to move a full vertical row of containers over the open portal. The containers can promptly drop through the portal and into a container chute 2150.

[71] In an exemplary embodiment, for a 1 inch diameter x 2 inch high 10 ml glass vial with a 20 mm opening, the outside carousel dimensions can be about 10 inch diameter x 10 inches high. This carousel can have 25 vertical slots, each holding 6 vials and thereby can hold a total of 150 vials. One additional, empty or blank slot can be included to enable the carousel to be transported without vials dropping through the portal. Other sizes and modifications are possible.

[72] Container chute 2150 can reorient (if necessary) containers arriving from the container supply subsystem 2100. Container chute 2150 can also protect the open containers from handling and contaminants. Container chute 2150 can be installed onto frame 2800 prior to sterilization of frame 2800. Container chute 2150 can be in place prior to the attachment of container supply subsystem 2100.

[73] Container chute 2150 can be shaped to accommodate each size of container used. Container chute 2150 can be manufactured of solid or welded stainless steel, such as type 316L, if container chute 2150 will be steam sterilized. Other materials of suitable strength and rigidity may be substituted.

[74] Container chute 2150 can present the containers to a container transport subsystem 2300 that transports the containers through a critical zone 2200 within which the containers can be filled and/or at least partially closed while an interior of the container is directly exposed to the airflow.

[75] Container positioner and/or container transport subsystem 2300 can transport containers to, through, and/or from a series of various processing stations, such as a container entry position 2330, a container fill position 2340, a container first closure affixing position 2350, a container dwell position 2360, a container second closure affixing position 2370, and/or a container exit position 2380, etc.

Among the many other potential stations (not shown) include stations for weighing, gas purging, closure providing, closure applying, closure inserting, overcapping, container diverting, lyophilization, filler inspection, head-space inspection, machine vision inspection, and/or labeling, etc. Upon exiting container transport subsystem 2300, a container can enter a container discharge chute 2700, which can lead to a filled container storage subsystem, a filled container lyophilization subsystem, and/or a filled container packaging subsystem, etc.

[76] Container transport subsystem 2300 can impart directionally and temporally controlled motion to the containers via any of a wide variety of devices, such as vacuum-assisted container grippers, air jets, a conveyor, a starwheel, a disk, an auger device, and/or a Rivard shuttle, etc. That motion can be intermittent and/or continuous. Container transport subsystem can be powered non-electrically, such as magnetically and/or fluidically (e.g., hydraulically and/or pneumatically), by for example, one or more pneumatic slave cylinders that are each coupled to a pneumatic master cylinder or actuator via one or more lengths of pneumatic tubing. Any of the lengths of tubing can be manually disassembleable without tools, sterilizable, decontaminateable, and/or disposable.

[77] In certain exemplary embodiments, a Rivard shuttle 2310 having a plurality of shuttle pins 2320 is implemented. At least a portion of Rivard shuttle 2310 can be located in and/or immediately adjacent critical zone 2200 and can move the vertical containers from the outlet of container supply chute 2150 and advance them through the series of processing stations. Rivard shuttle 2310 can be powered non-electrically, such as hydraulically and/or pneumatically, by for example, a pneumatic actuator 2390, which can comprise a sterilizable pneumatic cylinder.

[78] Rivard shuttle 2310 can provide an open architecture and/or an absence of gears and/or hinges. In operation, Rivard shuttle 2310 can allow the containers to travel along a stationary rail that can be perforated to facilitate laminar airflow and/or avoid adding substantial impediments and/or turbulence to the airflow. The containers can be advanced by a rod having notches on one side for the container to seat into. Inserted perpendicularly into the rod behind each notch

can be a shuttle pin 2320 that can prod an adjacent container along the rail when the rod is slid in a forward direction. When the container has reached the next station, the rod can rotate 90 degrees along its axis. When this occurs, the shuttle pins are now pointed down (or upward if desired), thereby disengaging from their adjacent containers, and the containers can be bumped slightly away from the rod as the notches also rotate down with the pins and the full surface of the rod now contacts the container. The containers can seat into slight notches in a guardrail at each station. While the container remains at a particular station, the rod can slides in a reverse direction. The rod can then rotate 90 degrees along its axis, which can return the pins to the horizontal position. The rod is now prepared to move in a forward direction again. When the rod moves in the forward direction, the pins bump the containers out of the slight notches at each station and prod the containers along to the next station.

[79] At least container entry position 2330, container fill position 2340, and container first closure affixing position 2350 can be located in and/or adjacent critical zone 2200, the airflow upstream of which can be substantially shielded from other mechanical components of system 2000 and/or other systems. Exterior shield 2420 and/or interior shield 2440 can be substantially solid, clear, and/or formed of a material such as glass or plastic (e.g. plexiglass, polycarbonate, etc.). Either of shields 2420, 2440 can comprise appropriate ports for the entry into, and/or immediately adjacent, critical zone 2200 of unfilled containers, filling needle 2460, closures, and/or the discharge from critical zone 2200 of filled containers. Other ports may be provided for other purposes. Either of shields 2420, 2440 can prevent contaminants from entering the critical zone perpendicularly to the airflow.

[80] Filling needle 2460 can be mounted directly on to a critical zone shield 2420, 2440 and/or some other rigid surface. For pharmaceutical purposes, filling needle 2460 can be constructed of high-grade stainless steel, suitable for autoclaving. Filling needle 2460 can be attached to shield 2420, 2440, etc. prior to autoclaving to avoid handling after sterilization and the risk of contamination. Filling needle 2460 can be disposable to avoid cleaning issues. Filling needle can be coupled via one or more lengths of tubing to a filling pump. Any of the lengths of tubing can be disassembleable without tools, sterilizable, and/or

disposable. Filling can be automatically and/or intermittently supplied through filling needle 2460 to the containers that pass a filling station with which filling needle 2460 is associated.

[81] System 2000 can comprise a first closure storage apparatus 2500, and potentially a second closure storage apparatus 2600, each of which can hold and protect sterile closures. These closures may be rubber stoppers, syringe plungers, screw caps, and/or over-caps, etc. Thus, there can be multiple closure carousels when a closure system contains more than one part, such as for example, a stopper and over-cap. Because each closure storage apparatus can be preloaded and covered prior to sterilization, the closures and/or containers can be protected from handling and environmental contaminates.

[82] In certain exemplary embodiments, any closure storage apparatus 2500, 2600 can be implemented as a carousel, hopper, and/or vibrating bowl feeder, etc. An exemplary carousel can be constructed using two pieces, a rack and a cover. The carousel can hold between about 1 and about 1000 closures, including all values and subranges therebetween. The closures can be pre-loaded onto the carousel and the entire carousel covered prior to sterilization. If constructed of appropriate materials, the carousel can be moist heat sterilized to about 121 degrees C. Once sterilized, the carousel can be place onto a closure carousel plate of system 2000.

[83] A closure carousel can be milled from a solid cylinder of aluminum, however, Teflon, welded 16-gage stainless steel sheet (such as type 316L), or other materials of suitable strength and rigidity may be substituted. The carousel can be ringed with vertical slots that can hold closures. The base of the carousel can be a solid disk except for one portal on the bottom that can allow the closures to drop through. After a vertical row has emptied of closures, the carousel can index to move a full vertical row of closures over the open portal. The closures can promptly drop through he portal and into a closure chute 2520, which can deliver the closures to a closure provider/applier/inserter 2540, 2640.

[84] In an exemplary embodiment, for a 20 mm diameter standard rubber stopper, the outside carousel dimensions can be about 10 inch diameter x 10 inches high. This carousel can have about 20 vertical slots, each holding 13 stoppers and thus holding a total of about 260 stoppers. One additional, empty, and/or blank slot

can be included to enable the carousel to be transported without stoppers dropping through the portal. Other sizes and modifications are possible for the carousel, stoppers, syringe plungers, screw caps, and/or over-caps.

[85] Closure chute 2520 can orient and/or reorient (if necessary) closures arriving from the closure storage apparatus 2500. Closure chute 2520 can protect the closures from handling and contaminants. Closure chute 2520 can be placed and/or attached onto frame 2800 prior to sterilization of frame 2800. Therefore, closure chute 2520 can be in place prior to the attachment of the closure storage apparatus 2500. In certain exemplary embodiments, each closure storage apparatus can have one or more closure chutes 2520 associated therewith. In certain exemplary embodiments, multiple closure storage apparatus 2500, 2600 can share a single closure chute 2520.

[86] Closure chute 2520 can be shaped to accommodate each size of closure used. Closure chute 2520 can be manufactured of solid or welded stainless steel, such as type 316L, if the container chute will be steam sterilized. Other materials of suitable strength and rigidity may be substituted. These include Teflon and aluminum, for example. Surfaces of closure chute 2520 can be smooth and slope adjusted to assure that the closures are consistently presented to the closure provider/applier/inserter 2540, 2640.

[87] Each closure provider/applier/inserter 2540 can obtain and/or lift a closure from its closure chute 2520, deposit the closure on a container, partially insert the closure into the container, fully insert the closure into the container, affix the closure to the container, crimp the closure, etc. In certain exemplary embodiments, a single device provides each desired function, however, other embodiments may utilize a separate device for certain functions. In the illustrated embodiment, a first closure provider/applier/inserter 2540 affixes a first closure, such as a stopper, to a container, and a second closure provider/applier/inserter 2640, affixes a second closure, such as an overcap, to the first closure.

[88] Each closure provider/applier/inserter 2540, 2640 can possess an absence of joints or other Class 100, 1000, and/or 10,000 particulate generators and/or contaminant generators in the critical zone and/or the airflow upstream of the critical zone.

[89] Each closure provider/applier/inserter 2540, 2640 can be manufactured from stainless steel, such as type 316L stainless steel, however, other suitable materials may be utilized. Each closure provider/applier/inserter 2540, 2640 can be operated non-electrically, such as via pneumatics, which can control the specific movements of the closure provider/applier/inserter. In certain exemplary embodiments, the closure provider/applier/inserter can be hollow, with a hole located underneath the tip, pointing down. A vacuum can be drawn through the closure provider/applier/inserter that can lift the closure off the closure chute. The closure provider/applier/inserter can be pneumatically raised while remaining horizontal. When higher than the level of the container, the closure provider/applier/inserter can advance forward, through a port in interior shield 2440, until the suspended closure is directly above the open container. The closure provider/applier/inserter then can be lowered until it affixes the closure upon the open container. The vacuum can be shut off, and the closure inserter can be raised up, retracted, and then lowered to grasp the next closure.

[90] Upon exiting Rivard shuttle 2300, containers can enter a container discharge chute 2700 that can accumulates containers and/or deliver containers to a next processing station. Container discharge chute 2700 can be pitched slightly down and away from the exit of the Rivard Shuttle to allow for easier movement as the containers crowd in. Container discharge chute 2700 can mount with vertical pins on the bottom of container discharge chute 2700 that can allow container discharge chute 2700 to be easily placed on and/or removed from frame 2800.

[91] **FIG. 3** is a front view of an exemplary embodiment of a system 3000, which can comprise a critical zone 3200, an operation zone 3250, container transport subsystem 3300, and/or a frame 3800, etc. An airflow 3900 can proceed relatively unimpeded by system 3000.

[92] Container transport subsystem 3300 can transport containers through a series of various processing stations, such as a container entry position 3330, a container fill position 3340, a container first closure affixing position 3350, a container dwell position 3360, a container second closure affixing position 3370, etc.

[93] Container transport subsystem 3300 can comprise a Rivard shuttle 3310 having a plurality of shuttle pins 3320. At least a portion of Rivard shuttle 2310 can be located in and/or immediately adjacent critical zone 3200. Rivard shuttle 2310

can be powered non-electrically, such as hydraulically and/or pneumatically, by for example, a pneumatic actuator 3390, which can comprise a sterilizable pneumatic cylinder.

[94] **FIG. 4** is a block diagram of an exemplary embodiment of an information device 4000, which can represent information device 1700 of FIG. 1. Information device 4000 can include well-known components such as one or more communications interfaces 4100, one or more processors 4200, one or more memories 4300 containing instructions 4400, one or more input/output (I/O) devices 4500 coupled to one or more user interfaces 4600, etc.

[95] As used herein, the term "information device" means any device capable of processing information, such as any general purpose and/or special purpose computer, such as a personal computer, workstation, server, minicomputer, mainframe, supercomputer, computer terminal, laptop, wearable computer, and/or Personal Digital Assistant (PDA), mobile terminal, Bluetooth device, communicator, "smart" phone (such as a Handspring Treo-like device), messaging service (e.g., Blackberry) receiver, pager, facsimile, cellular telephone, a traditional telephone, telephonic device, programmable logic controller (PLC), a programmed microprocessor or microcontroller and/or peripheral integrated circuit elements, an ASIC or other integrated circuit, a hardware electronic logic circuit such as a discrete element circuit, and/or a programmable logic device such as a PLD, PLA, FPGA, or PAL, or the like, etc. In general any device on which resides a finite state machine capable of implementing at least a portion of a method, structure, and/or or graphical user interface described herein may be used as an information device.

[96] As used herein, the term "communications interface" means any device, system, or subsystem capable of coupling an information device to a network and/or another information device. For example, a communications interface can be a telephone, cellular phone, cellular modem, telephone data modem, fax modem, wireless transceiver, infrared transceiver, ethernet card, cable modem, serial communications port, parallel communications port, PCMCIA slot and/or card, digital subscriber line interface, bridge, hub, router, or other similar device. Data and/or instructions transferred via a communications interface can be in the form of signals, which may be electronic, electromagnetic, optical, and/or other

signals capable of being received by a network interface. Such signals can be provided to a network interface via a communications path (i.e., channel), which can be implemented using wire or cable, fiber optics, a phone line, a cellular phone link, an RF link, an infrared link, and/or other communications media.

[97] As used herein, the term "processor" means a device for processing machine-readable instruction. A processor can be a central processing unit, a local processor, a remote processor, parallel processors, and/or distributed processors, etc. The processor can be a general-purpose microprocessor, such the Pentium III series of microprocessors manufactured by the Intel Corporation of Santa Clara, California. In another embodiment, the processor can be an Application Specific Integrated Circuit (ASIC) or a Field Programmable Gate Array (FPGA) that has been designed to implement in its hardware and/or firmware at least a part of an embodiment disclosed herein.

[98] As used herein, a "memory device" means any hardware and/or firmware element capable of storing data and/or instructions. Memory devices can comprise non-volatile memory, volatile memory, Random Access Memory, RAM, Read Only Memory, ROM, PROM, EPROM, EEPROM, flash memory, magnetic media, a hard disk, a floppy disk, a magnetic tape, an optical media, an optical disk, a compact disk, a CD, a digital versatile disk, a DVD, and/or a raid array, etc. A memory device can be removable, can include an interface (such as a drive, controller, socket, driver software, etc.), and/or can function as a computer-readable medium and/or as a machine-readable medium.

[99] As used herein, the term "firmware" means machine-readable instructions that are stored in a read-only memory (ROM). ROM's can comprise PROMs, EPROMs, and EEPROMs.

[100] As used herein, the term "I/O device" means any device capable of providing input to, and/or output from, an information device. An I/O device can be any sensory-oriented input and/or output device, such as an audio, visual, tactile (including temperature, pressure, pain, texture, etc.), olfactory, and/or taste-oriented device, including, for example, a monitor, display, keyboard, keypad, touchpad, pointing device, microphone, speaker, video camera, camera, scanner, and/or printer, potentially including a port to which an I/O device can be attached or connected.

[101] As used herein, the term "user interface" means any device for rendering information to a user and/or requesting information from the user. A graphical user interface can include one or more elements such as, for example, a window, title bar, panel, sheet, tab, drawer, matrix, table, form, calendar, outline view, frame, dialog box, static text, text box, list, pick list, pop-up list, pull-down list, menu, tool bar, dock, check box, radio button, hyperlink, browser, image, icon, button, control, dial, slider, scroll bar, cursor, status bar, stepper, and/or progress indicator, etc. An audio user interface can include a volume control, pitch control, speed control, voice selector, voice recognition module, speech controller, etc.

[102] In certain exemplary embodiments, user interface 4600 of information device 4000 can provide one or more elements for programming, monitoring, alerting, adjusting, and/or logging any activity of any component of any of systems 1000, 2000, and/or 3000, such as for example, the source of the airflow, the pump, and/or the pneumatic cylinders (which can actuate the Rivard shuttle, a carousel, and/or a closure inserter, etc.), etc. For example, via user interface 4600 of information device 4000, the step sequence can easily be set and/or manipulated to control the timing of each step. If sensors are used, such as on the pneumatic cylinders, information device 4000 can monitor each pneumatic action and/or activate the pump at the appropriate time.

[103] In certain exemplary embodiments, user interface 4600 can provide a live operational status window of various operational parameters; control of process instrumentation operation on-the-fly; and/or control of multiple filling systems and/or subsystems.

[104] **FIG. 5** is a flow chart of an exemplary embodiment of a method 5000. At activity 5100, containers and/or closures can be loaded and/or preloaded. The containers and/or closures can be sterile. Activity 5200, a container can be shielded from contaminants while outside and/or inside a critical zone. At activity 5300, a container can be positioned at a desired station, such as a station for purging, filling, closing, crimping, and/or lyophilizing, etc. The station can be located in and/or immediately adjacent a critical zone positioned in an airflow encountering no Class 100, 1000, and/or 10,000 contaminant generators upstream from the critical zone. At activity 5400, a filling can be introduced to

the container via a filling inlet (e.g., mouth, top, etc.) of the container. At activity 5500, one or more closures can be affixed to the container. Any one or group of activities 5100 through 5500 can be repeated as desired. Any one or group of activities 5300 through 5500 can be performed in isolation from a human operator and/or contaminants.

[105] At activity 5600, the system can be manually disconnected, such as from any pumping system and/or non-electrical power system (e.g., pneumatic connections). At activity 5700, the system can be manually loaded into a sterilization and/or decontamination device, such as an autoclave. At activity 5800, the system can be sterilized and/or decontaminated. At activity 5900, the system can be manually connected, such as to a pumping system and/or non-electrical power system, such that the system can be operational again, and any one or group of activities 5100 through 5900 can be repeated as desired.

[106] **FIG. 6** is a top view of an exemplary embodiment of a container positioning system 6000, which can comprise a Rivard shuttle 6100 having a rod 6200, a stationary rail 6300, and/or a guardrail 6400. Integrated into container positioning system 6000 and/or adjacent thereto can be a container entrance chute 6600 and/or a container exit chute 6700. Rod 6200 can comprise notches 6220 and/or shuttle pins 6240 that can engage with containers at and/or between various processing stations. Stationary rail 6300 can define holes 6320 to allow the airflow to pass therethrough. Guardrail 6400 can comprise notches 6420 that can engage with containers at various processing stations.

[107] **FIG. 7** is a front view of an exemplary embodiment of a Rivard shuttle 6100, such as that shown in FIG. 6. **FIG. 8** is a top view of an exemplary embodiment of a stationary rail 6300, which can define holes 6320 to allow the airflow to pass therethrough. **FIG. 9** is a top view of an exemplary embodiment of a guardrail 6400, which can comprise notches 6420 that can engage with containers at various processing stations. **FIG. 10** is a top view of an exemplary embodiment of a rod 6200, which can comprise notches 6220 and/or shuttle pins 6240 that can engage with containers at and/or between various processing stations.

[108] What follows is an exemplary operation sequence for certain exemplary embodiments of an asceptic processing system ("machine") described herein.

Set-Up:

[109] Close the air system dump valve to supply air to a pneumatic power system 1800. Supply air pressure can be about 80-100 PSI. Regulated air pressure to the pneumatic power system 1800 can be approximately 60-80 PSI.

[110] Regulated air pressure to each pneumatically-driven component of the machine can read approximately as follows:

[111] Shuttle Travel—30 PSI

[112] Shuttle Pin Rotate—20 PSI

[113] Vial Turntable—60 PSI

[114] Vial Turntable Cam—60 PSI

[115] Stopper Pick-up Plate—40 PSI

[116] Stopper Pick-up Plate Cam—60 PSI

[117] Stopper Insertion—40 PSI

[118] Stopper Arm Rotate—20 PSI

[119] Stopper Pick-up Vacuum—60 PSI

[120] With air pressure supplied to the machine, any of the pneumatic cylinders may be cycled by pressing the manual over-ride button on the pneumatic console for that cylinder.

[121] Plug-in the machine to a 120V 60Hz 20A power source.

[122] Load the stopper bin with about 500 stoppers.

[123] Load the vial turntable with one tray of vials, remove the tray and place a second tray in the load position, and so on to keep the turntable loaded with vials during operation.

Power On:

[124] Twist to release the Power button. The button will illuminate RED and electrical power will be supplied to the machine.

[125] Switch the power button on the laptop to the ON position and its display will illuminate.

[126] Open the air valve to supply air to the machine.

[127] The pneumatic components of the machine will move to their home positions.

Manual Single Step Mode:

[128] With the machine stopped, press the Single Step button on the laptop display. Starting with the first step in the sequence of operation, the machine will proceed through one step of the sequence at time each time the button is pressed. The pump fill cycle will not be started during the Single Step Mode.

Cycle Pump:

[129] With the machine stopped, press the Cycle Pump button to start the pump fill cycle. Note: a vial must be in position for the pump to cycle. Only the pump will operate and when the cycle is complete, the machine will wait for the next command from the operator.

Single Cycle Mode:

[130] With the machine stopped, press the Single Cycle button on the laptop display. Press YES or NO to confirm whether or not the pump fill cycle is to be started as the machine runs. Starting with the first step in the sequence of operation, the machine will proceed through one complete cycle and then stop. One complete cycle will be made each time the Single Cycle button is pressed.

Automatic Run Mode:

[131] With the machine stopped, press the Run button. Press the YES or No to confirm whether or not the pump fill cycle is to be started as the machine runs. The machine will begin normal operation and will continue until stopped by the operator, stopped by a shortage of vials or stoppers, or stopped by a condition which has prevented a sensor from supplying an expected input when needed in the sequence (see diagnostics).

Normal Sequence of Operation:

[132] At power-up all cylinders will move to the home position, as follows:

[133]	Pneumatic Cylinder	Position	Sensor Input On
[134]	Shuttle Pin Rotate	Extended	On
[135]	Shuttle Travel	Retracted	On
[136]	Vial Turntable	Retracted	On

[137]	Vial Turntable Cam	Retracted	On
[138]	Stopper Pick-up Plate	Retracted	On
[139]	Stopper Pick-up Plate Cam	Retracted	On
[140]	Stopper Insertion	Retracted	On
[141]	Stopper Rotate	Extended	On
[142]	Stopper Pick-up Vacuum	Off	N/A

[143] Input sensors will indicate key machine conditions, as follows:

[144]	Vial Present	Off
[145]	Stopper Present	Off
[146]	Stopper Queue	Off

[147] When the Run Mode is selected, the following events occur automatically (these events may be selected one at a time by using the Single Step Mode):

[148] The vial turntable cam cylinder will extend to set the cam against the turntable drive plate. The vial turntable cylinder will extend causing the turntable to rotate. When the turntable cylinder has reached the end of its stroke, the cam cylinder will retract and then the turntable cylinder will retract. These events will continue repeatedly while the machine is in run mode to bring vials to the queue position of the shuttle. (Note: the vial turntable cylinder typically should finish retracting and start extending prior to the shuttle travel cylinder extending. This will keep pressure against the next vial to be picked-up by the shuttle at the time of pick-up.)

[149] The stopper pick-up plate cam cylinder will extend to set the cam against the stopper pick-up drive plate. The stopper pick-up plate cylinder will extend to rotate causing stoppers to be picked-up and allowing stoppers to fill the dispensing chute. When the pick-up plate cylinder has reached the end of its stroke, the cam cylinder will retract and then the pick-up plate cylinder will retract. When the dispensing chute is filled with enough stoppers, the Stopper Queue Input sensor will illuminate On causing the stopper pick-up plate to stop rotation at the end of its cycle. When this sensor no longer detects the presence of stoppers in the dispensing chute, rotation of the stopper pick-up plate will resume immediately.

[150] When stoppers reach the bottom of the stopper dispensing chute, the stopper present input sensor will illuminate On indicating that a stopper is present and the stopper components of the machine are ready for a vial.

[151] With the stopper present sensor on, the shuttle pin rotate cylinder retracts causing the pins on the shuttle rod to rotate to the up (push) position.

[152] The shuttle travel cylinder extends causing the shuttle to index a vial from the queue position to the fill position.

[153] The shuttle pin rotate cylinder extends causing the shuttle pins to rotate to the down position. This positions the vial in its nest for filling or for stopper insertion, and allows the shuttle travel rod to return to the home position to pick-up the next vial.

[154] The vial present input sensor illuminates when a vial is present, causing an output to the pump to begin the pre-programmed pump fill cycle. (If no vial is present, there is no input and the pump is not started. The vial present input sensor looks for a vial on the next index of the shuttle. If no vial was filled, then no attempt will be made to insert a stopper on the next index of the shuttle. If no vial is present on the third index of the shuttle, the run cycle will stop and an alarm will appear on the laptop display.)

[155] The shuttle travel cylinder retracts returning the shuttle to pick-up the next vial. (Note: with the pins in the down position, the shuttle can return to the home position while the pump cycle is in progress.)

[156] When the pump fill cycle has finished, the shuttle pin rotate cylinder retracts causing the pins to rotate to the up position; and the shuttle travel cylinder extends to move an empty vial from the queue position to the fill position and to move a filled vial from the fill position to the stopper position.

[157] If a vial is present the pump fill cycle is started.

[158] If a vial was filled on the previous cycle, a stopper is placed on the filled vial as follows (these actions are taking place while the vial is being filled so that the stopper is waiting over-top of the filled vial as it moves into the stopper position on the shuttle).

[159] The stopper insert cylinder extends to pick-up a stopper.

[160] Vacuum is turned On

[161] The stopper insert cylinder retracts.

[162] The stopper rotate cylinder extends to position the stopper insert arm over the filled vial.

[163] The stopper insert cylinder extends to press the stopper onto the filled vial.

[164] Vacuum is turned Off.

[165] The stopper insert cylinder retracts.

[166] The stopper rotate cylinder retracts and is ready to pick-up the next stopper.

[167] When the pump fill cycle is finished the shuttle indexes to move another vial from the queue position to the fill position, to move a filled vial from the fill position to the stopper position, and to move a stoppered vial from the stopper position toward the shuttle discharge position where the vial moves from the shuttle into a collection tray.

[168] A total count is maintained of vials filled during the run.

[169] A cycle count of filled vials is made to determine when the number of vials needed to complete a tray has been filled. When this number of vials has been filled and has been indexed to the discharge position, the machine will stop until the operator replaces the tray and presses the Batch Complete button and then the Automatic button to resume processing. Note: the machine will pause prior to the fill cycle of the next vial so a filled vial does not wait exposed to air while the tray is being changed. At the end of a run, vials remaining in the shuttle can be lifted out or cleared by running the Single Step Mode.

Shut-Down:

[170] Press the POWER button to turn the system off. This button kills all electrical power to the machine.

[171] Still other embodiments will become readily apparent to those skilled in this art from reading the above-recited detailed description and drawings of certain exemplary embodiments. It should be understood that numerous variations, modifications, and additional embodiments are possible, and accordingly, all such variations, modifications, and embodiments are to be regarded as being within the spirit and scope of the appended claims. For example, regardless of the content of any portion (e.g., title, field, background, summary, abstract, drawing figure, etc.) of this application, unless clearly specified to the contrary,

there is no requirement for the inclusion in any claim of the application of any particular described or illustrated activity or element, any particular sequence of such activities, or any particular interrelationship of such elements. Moreover, any activity can be repeated, any activity can be performed by multiple entities, and/or any element can be duplicated. Further, any activity or element can be excluded, the sequence of activities can vary, and/or the interrelationship of elements can vary. Accordingly, the descriptions and drawings are to be regarded as illustrative in nature, and not as restrictive. Moreover, when any number or range is described herein, unless clearly stated otherwise, that number or range is approximate. When any range is described herein, unless clearly stated otherwise, that range includes all values therein and all subranges therein. Any information in any material (e.g., a United States patent, United States patent application, book, article, etc.) that has been incorporated by reference herein, is only incorporated by reference to the extent that no conflict exists between such information and the other statements and drawings set forth herein. In the event of such conflict, including a conflict that would render a claim invalid, then any such conflicting information in such incorporated by reference material is specifically not incorporated by reference herein.